REMARKS

Claims 41-46 have been amended.

New Claims 89-94 have been added.

Claim 41, as amended, is directed to a method of using a specific metabolic phenotype to individualize a treatment regimen for a class N-(aryl substituted)-naphthalimide compound for an individual in need thereof comprising: a) characterizing the specific metabolic phenotype of said individual; and b) determining a safe and therapeutically effective dose of said class N-(aryl substituted)-naphthalimide compounds compound for said individual based directly on said specific metabolic phenotype of said individual and at least one other specific characteristic for said individual, thereby individualizing the treatment regimen for said individual. Support for the amendment to Claim 41 is found in the specification, for example, at page 66, lines 16-20; page 74, lines 11-15; page 215, line 3 to page 216, line 2; and page 237, lines 21-28; and Example III.

Claim 42, as amended, is directed to the method of claim 41, wherein said class N-(aryl substituted)-naphthalimide compound is amonafide. Support for the amendment to Claim 42 is found in the specification, for example, at page 56, lines 17-26, and page 66, lines 16-25.

Claim 44, as amended, is directed to a method of treating an individual having a condition treatable with a class N-(aryl substituted)-naphthalimide compound, said method comprising: a) determining the specific metabolic phenotype of said individual; and b) administering a safe and therapeutically effective dose of said class N-(aryl substituted)-naphthalimide compound to said individual, wherein said dose has been determined based directly on said individual's specific metabolic phenotype for said class N-(aryl substituted)-naphthalimide compound individual and at least one other specific characteristic for said individual. Support for the amendment to Claim 44 is found in the specification, for example, at page 56, lines 4-16; page 74, lines 11-15; page 215, line 3 to page 216, line 2; page 237, lines 21-28; and Example III.

Claim 45, as amended, is directed to the method of claim 44, wherein said class N-(aryl substituted)-naphthalimide compound is amonafide. Support for the amendment to Claim 45 is found in the specification, for example, at page 56, lines 17-26, and page 66, lines 16-25.

Claims 43 and 46, as amended, recited "specific" metabolic phenotype and "compound". Support for the amendment to Claims 43 and 46 is found in the specification, for example, at page 54, lines 25-30 and page 56, line 27 to page 57, line 11.

New Claim 89 is directed to the method of Claim 41, wherein the metabolic phenotype is characterized by quantifying a ratio of detected metabolites for the probe substrate in the sample, and wherein the dose is determined directly from this ratio. Support for new Claim 89 is found in the specification, for example, at page 51, lines 14-18; page 55, line 10 to page 58, line 18; page 60, lines 4-15; page 62, line 20 to page 63, line 6; page 66, lines 16-29; Table 4 at page 143; and Examples I-III.

New Claim 90 is directed to a method of using a metabolic phenotype to individualize a treatment regimen for a class N-(aryl substituted)-naphthalimide compound for an individual in need thereof comprising: a) administering to an individual amonafide; b) detecting metabolites of amonafide in a biological sample from said individual in response to administered amonafide; c) characterizing the specific metabolic phenotype of said individual by quantifying a ratio of detected metabolites for said amonafide in the sample; and d) determining a safe and therapeutically effective dose of said class N-(aryl substituted)-naphthalimide compound for said individual based directly on said specific metabolic phenotype individual and at least one other specific characteristic for said individual, thereby individualizing the treatment regimen for said individual. Support for new Claim 90 is found in the specification, for example, at page 55, lines 16-25; page 78, lines 2-5; page 215, line 3 to page 216, line 2; page 237, lines 21-28 and Examples I-III.

New Claim 91 is directed to a method of treating an individual having a condition treatable with a class N-(aryl substituted)-naphthalimide compound, said method comprising: a) administering to an individual amonafide; b) detecting metabolites of amonafide in a biological sample from said individual in response to administered amonafide; c) determining the specific metabolic phenotype of said individual by quantifying a ratio of detected metabolites for said amonafide in the sample; and d) administering a safe and therapeutically effective dose of said class N-(aryl substituted)-naphthalimide compound to said individual and at least one other specific characteristic for said individual, wherein said dose has been determined based directly on said specific metabolic phenotype, thereby individualizing treatment for said individual.

Support for new Claim 91 is found in the specification, for example, at page 55, line 10 to page 56, line 3; page 78, lines 2-5; page 215, line 3 to page 216, line 2; page 237, lines 21-28 and Examples I-III.

New Claim 92 is directed to the method of Claim 41, wherein said probe substrate is amonafide. Support for new Claim 92 is found in the specification, for example, at page 78, lines 2-5.

New Claim 93 is directed to the method of Claim 44, wherein said probe substrate is amonafide. Support for the New Claim 93 is found in the specification, for example, at page 78, lines 2-5.

New Claim 94 is directed to the method of Claim 41, wherein said specific characteristic is selected from the group consisting of age, gender and white blood cell count. Support for the New Claim 94 is found in the specification, for example, at page 19, lines 26-27; page 215, line 3 to page 216, line 2; and page 237, lines 21-28.

No new matter has been added by the amendments. Therefore, entry of the amendments into the application is respectfully requested.

Rejection of Claims 41-46 Under 35 U.S.C. § 102(b) as being anticipated by Ratain *et al.*

The Examiner has rejected Claims 41-46 under 35 U.S.C. § 102(b) as being anticipated by Ratain *et al.*, Cancer Research, 53:2304-2308 (1993). The Examiner states that:

> Ratain et al. teach a method of metabolic phenotyping to individualize amonafide dosage. Ratain et al. determined the acetylator phenotype of cancer patients in need of amonafide therapy, using caffeine as the probe drug and urine as the biological sample.... Dosage regimen of amonafide was individualized based on this phenotype, where the initial dose levels for slow, indeterminate, and fast acetylators were 375, 300, or 250 mg/m^2 (for 5 days), respectively. (See Amonafide Dosing, p. 2304).

Applicant respectfully disagrees. Claims 41-46 have been amended. Ratain *et al.* do not expressly or inherently disclose the claimed invention. Claim 41, as amended, recites "a method of using a specific metabolic phenotype to individualize a treatment regimen for a class N-(aryl substituted)-naphthalimide compound for an individual in need thereof comprising: a) characterizing the specific metabolic phenotype of said individual; and b) determining a safe and therapeutically effective dose of said class N-(aryl substituted)-naphthalimide compounds

compound for said individual based *directly* on said specific metabolic phenotype of said individual and at least one other specific characteristic for said individual, thereby individualizing the treatment regimen for said individual." (emphasis added) Likewise, Claim 44, as amended, recites "a method of treating an individual having a condition treatable with a class N-(aryl substituted)-naphthalimide compound, said method comprising: a) determining a specific metabolic phenotype of said individual; and b) administering a safe and therapeutically effective dose of said class N-(aryl substituted)-naphthalimide compound to said individual, wherein said dose has been determined based *directly* on said individual's specific metabolic phenotype for said class N-(aryl substituted)-naphthalimide compound and at least one other specific characteristic for said individual." (emphasis added) Claims 42 and 45, as amended, recite "the method of claim [41 or 44], wherein said class N-(aryl substituted)-naphthalimide compound is amonafide." Claims 43 and 46, as amended, recite "specific" metabolic phenotype and "compound". Thus, Applicant teaches using a metabolic phenotype to *individualize* a treatment regimen for a class N-(aryl substituted)-naphthalimide compound, including amonafide, for an individual in need thereof. Applicant's invention provides for the individualization of dosing with a drug *in direct relation* to the quantitative value of an individual's molar ratio calculated during phenotyping. Accordingly, dosing can be individualized, rather than categorized, to account for an individual's specific capacity to metabolize the drug. (See, for example, page 74, lines 11-17 of the specification)

In contrast, Ratain *et al.* disclose a study to identify recommended doses of amonafide for the *categories* of slow acetylator phenotype and fast acetylator phenotype. More specifically, Ratain *et al.* disclose administering caffeine as a probe substrate to individuals with cancer, quantifying the ratio of detected metabolites in a biological sample from each individual in response to the probe substrate, and then *categorizing* the individuals as slow acetylator phenotype and fast acetylator phenotype in order to recommend a dose of amonafide for the categories of slow acetylator and fast acetylator. They also suggest a dosage for patients who cannot be phenotyped at all. (page 2307, col. 1)

As stated by the authors, "[t]he primary objective of the current study was to identify recommended phase II doses of amonafide for each of the genetically determined acetylator phenotypes." (Introduction at page 2304, col. 1) Further, "[t]he study was designed to enroll

patients in cohorts, based on acetylator phenotype." (page 2304, col. 2) "For slow acetylators, subsequent cohorts were intended to be dose escalated...." (page 2304, col. 2) "For fast acetylators, subsequent cohorts were reduced...." (page 2304, col. 2).

Ratain *et al.* do not expressly anticipate the claimed invention. All of the elements of the claimed invention must be found within a single reference in order to anticipate, either expressly or inherently, under 35 U.S.C. § 102. As stated in *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1379, 231 U.S.P.Q. 81, 90 (Fed. Cir. 1986), for example, "[i]t is axiomatic that for prior art to anticipate under §102 it has to meet every element of the claimed invention, and that such a determination is one of fact." Ratain *et al.* do not teach a method of characterizing the specific metabolic phenotype of the individual to *individualize* a selected safe and therapeutically effective drug treatment dosing regimen. Although Ratain *et al.* quantified the rate of metabolism of a probe substrate, they did not directly correlate or connect the specific rate of metabolism of the individual with *individualized* treatment.

Further, Ratain *et al.* do not inherently disclose the claimed invention. The Manual of Patent Examining Procedure (MPEP 8th edition, May 2004 revision, § 2112) articulates the requirements of a rejection based on inherency. Specifically, under the subheading "Examiner Must Provide Rationale for Evidence Tending to Show Inherency," the MPEP quotes a decision by the Board of Patent Appeals and Interferences in *Ex parte Levy*, 17 U.S.P.Q.2d 1461, 1464 (Bd. Pat. App. & Inter. 1990) (emphasis in original), which states:

> In relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic *necessarily* flows from the teachings of the applied prior art.

As explained by the MPEP, the Examiner in *Ex parte Levy* argued, without providing support, that a reference inherently included a limitation of the Appellants' invention. According to the MPEP, the Board of Patent Appeals and Interferences reversed the Examiner's decision because the examiner did not provide objective evidence or cogent technical reasoning to support the conclusion of inherency. See MPEP at page 2100-52.

Further, the doctrine of inherency is based on the necessary presence of an element described in a reference; it is not sufficient to establish that a presence of the element is a

probability or a possibility. For example, as is also stated in the MPEP at § 2112 (emphasis in original): The fact that a certain result or characteristic *may* occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic. (Citing *In re Rijckaert*, 9 F.3d 1531, 1534, 28 U.S.P.Q.2d 1955, 1957 (Fed. Cir. 1993).)

The Examiner has presented no evidence that Ratain *et al.* would necessarily calculate a specific metabolic phenotype of an individual to individualize a selected safe and therapeutically effective drug treatment dosing regimen for said individual. In fact, the authors categorized the acetylator phenotype as slow acetylator and fast acetylator.

Moreover, to qualify as an anticipatory reference, a reference must meet the requirement of enablement. As stated in the MPEP at § 2121.01:

> "In determining that quantum of prior art disclosure which is necessary to declare an applicant's invention 'not novel' or 'anticipated' within section 102, the stated test is whether a reference contains an 'enabling disclosure'...."

(Quoting *In re Hoeksema*, 399 F.2d 269, 158 USPQ 596 (CCPA 1968).

> The disclosure in an assertedly anticipating reference must provide an enabling disclosure of the desired subject matter; mere naming or description of the subject matter is insufficient, if it cannot be produced without undue experimentation.

(Citing *Elan Pharm. Inc. v. Mayo Foundation for Medical and Education Research*, 346 F.3d 1051, 1054, 68 USPQ2d 1373, 1376 (Fed. Cir. 2003).

In contrast to Applicant's disclosure, Ratain *et al.* do not teach how to practice Applicant's claimed invention of individualizing treatment of an individual based directly on the individual's specific metabolic phenotype and other specific characteristics of the individual.

Ratain *et al.* do not expressly or inherently disclose characterizing a specific metabolic phenotype of an individual to directly individualize a selected safe and therapeutically effective drug treatment dosing regimen for said individual. Thus, the rejected claims, as amended, are novel. Reconsideration and withdrawal of the rejection are respectfully requested.

Rejection of Claims 41-46 Under 35 U.S.C. § 102(b) as being anticipated by Wainer *et al.*

The examiner has rejected Claims 41-46 under 35 U.S.C. § 102(b) as being anticipated by Wainer *et al.* (U.S. Patent No.: 5,830,672). The Examiner states that:

> Wainer et al. teach a method for determining N-acetyltransferase (NAT2) phenotype using [an] enzyme linked immunosorbent assay (ELISA) kit to individualize therapy of drugs, including amonafide (col. 1, lines 8-14). The ELISA measures the molar ratio of caffeine metabolites in a urine sample (col. 3, lines 15-55; claims 1-3 and 5-10). The acetylation phenotype is based on this ratio, where patients with a ratio less than 1.80 are considered slow acetylators (col. 3, lines 55-58).

Applicant respectfully disagrees. Claims 41-46 have been amended. Wainer *et al.* do not disclose or enable the claimed invention. Claim 41, as amended, recites "a method of using a specific metabolic phenotype to individualize a treatment regimen for a class N-(aryl substituted)-naphthalimide compound for an individual in need thereof comprising: a) characterizing the specific metabolic phenotype of said individual; and b) determining a safe and therapeutically effective dose of said class N-(aryl substituted)-naphthalimide compounds compound for said individual based *directly* on said specific metabolic phenotype of said individual and at least one other specific characteristic for said individual, thereby individualizing the treatment regimen for said individual." (emphasis added) Likewise, Claim 44, as amended, recites "a method of treating an individual having a condition treatable with a class N-(aryl substituted)-naphthalimide compound, said method comprising: a) determining a specific metabolic phenotype of said individual; and b) administering a safe and therapeutically effective dose of said class N-(aryl substituted)-naphthalimide compound to said individual, wherein said dose has been determined based *directly* on said individual's specific metabolic phenotype for said class N-(aryl substituted)-naphthalimide compound and at least one other specific characteristic for said individual." (emphasis added) Claims 42 and 45, as amended, are dependent upon Claims 41 and 44, and, thus, contain the same limitations. Claims 43 and 46, as amended, recite "specific" metabolic phenotype and "compound".

Wainer *et al.* disclose the use of molar ratios of caffeine metabolites to determine the acetylation phenotype of the individual as follows: "Individuals with a molar ratio less than 1.80 are slow acetylators." (col. 3, lines 55-59) Under the introductory paragraph, "Field of the Invention", the authors suggest that the disclosed kit can be used to individualize therapy of

drugs and predict susceptibility to certain disease. However, as with Ratain *et al.*, Wainer *et al.* discloses the categorizing of patients into two categories: slow acetylators and fast acetylators. Nor is there any teaching, example or data regarding the determination and administration of an individualized dose of a drug to an individual.

Wainer *et al.* do not anticipate the claimed invention. As discussed above, generally, all of the elements of the claimed invention must be found within a single reference in order to anticipate, either expressly or inherently, under 35 U.S.C. § 102. Nowhere do Wainer *et al.* disclose a method of characterizing the specific metabolic phenotype of the individual to individualize a selected safe and therapeutically effective drug treatment dosing regimen based directly on the individual's specific metabolic phenotype and other specific characteristics of the individual.

In addition, Wainer *et al.* do not enable the claimed invention under 35 U.S.C. § 112, first paragraph. As stated in the MPEP at § 2121.01:

> "In determining that quantum of prior art disclosure which is necessary to declare an applicant's invention 'not novel' or 'anticipated' within section 102, the stated test is whether a reference contains an 'enabling disclosure'...."

(Quoting *In re Hoeksema*, 399 F.2d 269, 158 USPQ 596 (CCPA 1968).

> The disclosure in an assertedly anticipating reference must provide an enabling disclosure of the desired subject matter; mere naming or description of the subject matter is insufficient, if it cannot be produced without undue experimentation.

(Citing *Elan Pharm. Inc. v. Mayo Foundation for Medical and Education Research*, 346 F.3d 1051, 1054, 68 USPQ2d 1373, 1376 (Fed. Cir. 2003).

Nowhere do Wainer *et al.* describe how to make and or use the claimed invention.

Wainer *et al.* do not disclose or enable characterizing a metabolic phenotype of an individual to *individualize* a selected safe and therapeutically effective drug treatment dosing regimen for said individual. Thus, the rejected claims are novel. Reconsideration and withdrawal of the rejection are respectfully requested.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned.

Respectfully submitted,

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